Early Childhood Inhalant Allergen Sensitization

In Atopic Eczema

Running title: Inhalant Allergen Sensitization in AD

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ABSTRACT

Background: The aim of this cross-sectional study was to characterize differences in inhalant allergen sensitization among three age groups of children with atopic dermatitis (AD).

Methods: Sixty-one children (0.5-13 years) with moderate to severe AD were enrolled from an Immunodermatology Clinic and divided into 3 age groups (less than 2, 2-4 years, and greater than 4 years). They were evaluated by history, physical examination, RAST for common inhalant allergens, and total IgE. Thirty-three control patients were enrolled from the outpatient clinics and 57 from a pediatric emergency room.

Results: Inhalant allergen sensitization particularly to dust mite and cat allergens was significantly more prevalent among AD patients than controls ($p<0.001$) as measured by RAST. Under age 2, 38% of AD patients were sensitized to inhalants, and this percentage increased with each successive age group. Significant differences were seen at each age group when AD was compared to controls. Total serum IgE levels were also greatly elevated for each age group. Logistic regression revealed significant odds ratios for the association of AD with log IgE (O.R. 65, 95% CI 12-359), positive RAST (O.R. 13, 95% CI 3.7-49), eosinophil counts (O.R. 15, 95% CI 2.8-85), and family history of allergic disease (O.R. 24, 95% CI 7-86).

Conclusion: The results demonstrate that early aeroallergen sensitization in children with moderate to severe AD is predominantly to the indoor allergens mite and cat. The results suggest that controlled studies on avoidance of inhalant allergens in AD should be started in infancy.

Keywords: eczema, inhalant allergens, atopic dermatitis, sensitization, childhood, dust mite, cat

Abbreviations: RAST, radioallergosorbent test

GM, geometric mean

CI, confidence interval

AD, atopic dermatitis

INTRODUCTION

" Despite...evidence of the importance of inhalant allergens in atopic dermatitis, one still sees many patients in whom attention has been directed entirely to removal of offending food or to elimination of psychogenic or infectious factors without benefit in either instance to the patient," wrote Louis Tuft in 1948 in the Journal of Investigative Dermatology (1). Regardless of numerous advances over the last 45 years, the role of inhalant allergens in the pathogenesis of AD is still controversial. The role of food allergens in atopic dermatitis has been more readily accepted with the association demonstrated by extensive work by May, Bock, Sampson and others (2,3). The development of the double blinded placebo controlled food challenge has helped to establish a cause and effect relationship between the ingestion of foods and allergic skin responses (4,5). Challenge testing with inhalants in eczema has been more difficult; however the patch test using inhalant allergen provides a model of the way in which topical exposure could contribute to eczema (6,7). The question arises as to whether aeroallergen enters by inhalation or direct contact with the skin. A role for aeroallergen inhalation has been inferred since 50-80% of children with AD also develop allergic rhinitis and/or asthma (8,9,10). Recent work by Van Reijsen and others has demonstrated that aeroallergens penetrating through the skin can induce a T_H2 cellular response in AD patients (11). Furthermore Langerhans cells in the skin have been shown to express high affinity receptors for IgE in patients with AD who have elevated serum IgE levels(12). These studies strongly suggest that allergen entering through the skin could boost the

immune response as well as contribute to the skin rash. With increasing emphasis on the role of inhalant allergens in the pathogenesis of AD, few studies have considered the natural history of sensitization to these allergens and most suggest that sensitization occurs after 2-3 years of age (9,13,14). The purpose of the present cross-sectional study was to characterize aeroallergen sensitization in three age groups of children with atopic dermatitis and to contrast these with age-matched controls from two outpatient settings.

MATERIALS AND METHODS

Sixty-one children with atopic dermatitis were enrolled from the pediatric allergy and immmunodermatology clinics at the University of Virginia. Patients enrolled were from 6 months to thirteen years of age with a mean age of 4.1 years. The diagnosis of atopic dermatitis was made based on the criteria of Hanifin and Rajka following assessment by two physicians (15). Each patient had moderate to severe skin involvement. Evaluation of these patients included allergic history of the patient and their family as well as physical examination. Skin prick testing with *D. farinae* and *D. pteronyssinus* was done and considered positive if the wheal was 3mm greater than the negative control. Serum was assayed for total serum IgE and for IgE antibody by RAST. Thirty-three control patients (control group I) were enrolled from the general pediatric and subspecialty clinics. These patients were from 1 month to 15.9 years old (mean age of 5.4 years), and according to their history had never had eczema or related skin disorders. These patients were evaluated by questionnaire, serum samples for RAST and IgE, and complete blood counts. Fifty-seven control patients (control group II) were enrolled from the pediatric emergency room. They also gave a negative history for atopic dermatitis as well as asthma and were evaluated by questionnaire, serum for RAST, and total IgE analysis. Further studies done with control II patients are reported elsewhere (16).

Allergen-specific IgE to five common inhalant allergens (dust mite, cat, cockroach, rye grass, and ragweed) was measured using cyanogen bromide activated dics coated with

extracts from Hollister-Stier Laboratories, Inc., Spokane, Washington as previously described (17). Horse serum was used as a diluent to minimize non-specific binding. A positive RAST was defined as >40 RAST units/ml. The units are related to a serum pool obtained from the National Institute of Biological Standards and Control, London, UK (Code #NIBSC 82-528), which was used to establish a *D.farinae* control curve; this unit is equivalent to approximately 0.1ng IgE, thus 40 RAST units is ~4ng/ml of allergen-specific IgE antibody.

Total serum IgE was measured using a two-site monoclonal antibody-based enzyme immunoassay as previously described (monoclonal anti-Fc epsilon antibodies provided by Dr. Andrew Saxon) (18). Complete blood counts to assess total eosinophil counts were measured by peroxidase staining using a cell automated Technicon H1 system in the hospital clinical laboratories. The study was approved by the Human Investigation Committee at the University of Virginia, and all parents of patients gave consent to participate in this study. Statistical analysis was done to compare differences between the control and atopic dermatitis patients using paired T-tests and chi-square test. When samples were small Fishers exact test was used. Logistic regression models were used to assess the differences between AD patients and controls with respect to race, sex, family history, RAST positivity, IgE and eosinophil counts. Regression coefficients from these models were used to estimate odds ratios and 95% confidence intervals. All tests of significance were two tailed (19).

RESULTS

Demographics

No statistical differences were noted between controls and atopic dermatitis patients with regard to age, race, and sex. These results are summarized in Table 1.

Sensitization to Inhalant Allergen

Overall, 57% of AD patients compared to 9% of control I patients and 22% of control II patients were sensitized to one or more inhalant allergens as measured by RAST ($p<0.001$ for each group). Fifty percent of AD patients were sensitized to dust mite (Figure 1). When comparing AD patients in different age groups, a significant difference was seen in RAST positivity between those children less than 2 and those over 4 ($p<0.01$, Figure 2). In all three age groups, a significant difference was seen in specific IgE antibodies to inhalants between the control groups and the AD group. As judged by RAST results, sensitization to cat allergen was most frequently seen, with 33% of children under 2 being positive (Fig. 3). All children who were positive by RAST to dust mite were also positive by skin test; however, positive skin tests were present in five children under two years of age who had a negative RAST. Thus, by skin testing 41% of the AD children under two were positive to mite. In the older age group (over age 4) 73% of the AD children were sensitized to dust mite and there was an excellent correlation between RAST and skin tests.

In most patients who were positive to dust mite, their RAST specific IgE was very

elevated, with sixteen having values greater than two thousand (GM=1,919 units). On the average the levels of specific IgE to cat were lower with values in the hundreds of units (GM=305 units) (Figure 4). The levels of IgE ab to cat were very low in the controls with only 2 of 87 having a positive RAST. Among the six children with AD less than 2 years old who were positive to cat, 4 had >200 RAST units/ml.

Total IgE

Measurements of total IgE revealed statistical differences between AD patients and controls among all age groups. Among children under two, the GM of the total IgE for AD patients was 109 IU/ml (95% CI 47 to 253 IU/ml) compared to 3.6 IU/ml (95% CI, 1.4 to 9.4 IU/ml) for control group I and 4.2 IU/ml (95% CI, 1.8 to 9.6 IU/ml) for control group II. Patients with AD from two to four years of age showed GM IgE of 264.5 IU/ml (95% CI 109 to 647 IU/ml); comparable values for the two control groups were 14 IU/ml (95% CI, 5 to 39 IU/ml), and 3.2 IU/ml (95% CI, .8 to 12 IU/ml). This difference was even more pronounced in the patients over four, GM 911 IU/ml (95% CI, 468 to 1758 IU/ml) contrasted with 29 IU/ml (95% CI, 11 to 75 IU/ml) in control group I and 35 IU/ml (95% CI, 23.5 to 51 IU/ml) in control group II. Additionally, absolute eosinophil counts were obtained in a minority of AD patients and for control group I. In 22 AD patients, the mean eosinophil count was 483 /μl compared to 218 /μl in 33 control patients ($p<0.001$).

Odds Ratios

Several risk factors showed significant univariate odds ratios reflecting their importance in differentiating AD patients from control group I (Table 2). The strongest correlations were seen for log total serum IgE, family history, and positive RAST.

DISCUSSION

In this study we have demonstrated a high prevalence of IgE antibody to two indoor allergens (dust mite and cat) among children with AD. Furthermore the incidence of inhalant allergen sensitization among children less than two was higher than has been reported previously. Several studies have demonstrated the prevalence of inhalant sensitization among older children (9,13,14,20-22). There have also been case reports suggesting a cause and effect relationship between flares of atopic dermatitis and exposure to inhalant allergens (1,23). Other studies have reported a significant association between IgE ab responses to food allergens and moderate to severe atopic dermatitis (2,3,4,8,9,13). The patients enrolled in the present study were also evaluated for serum IgE antibodies by RAST to milk, soy, peanut, and wheat: in data not presented here, 84% percent of the patients under two were sensitized to one or more foods similar to values reported by others (24,9). Furthermore 38% of the children under 2 years of age had evidence of sensitization to both inhalants and food.

The levels of IgE antibody to dust mite allergen were very high with values of 100-1000 units/ml ~ equivalent to 10-100 ng IgE ab. Even in children less than two, the levels of specific IgE to mite were high in RAST positive patients (range 920-1680 units/ml). Although the levels of IgE antibody to cat allergen were lower in all patients, serum IgE ab to cat was present earlier with six children under two positive. However, judging by skin tests as well as RAST, sensitization to dust mite had also occurred in a large percentage of the very young. The discrepancy between skin test data and RAST

for dust mite suggests that skin sensitization occurs before a significant rise in serum titers.

Whether the differences between cat and mite sensitization as judged by RAST are related to differences in exposure is not clear. Mite allergen is carried on large particles which are not airborne unless disturbed and settle quickly (25). Cat allergen on the other hand is carried on small particles and is airborne even in undisturbed conditions (26). While some patients may sleep with cats, exposure is more likely to occur via inhalation. Bedding is known to be an important reservoir for mites, but this probably only applies to children over 2 years old since crib bedding is washed regularly and the mattresses are constructed with a plastic covering. It is possible that mite allergen exposure then enters through the skin, is presented via Langerhans cells, and that this route boosts IgE antibody production in the older children. It is also interesting to note the presence of pollen sensitization in some patients under two. Both of the children who had IgE ab to ragweed were born in July just prior to the ragweed season in Virginia. Numerous studies have suggested that the month of birth influences an infants risk of subsequent allergy development (27). However, overall levels of pollen sensitization in the AD patients were low which may reflect the decreasing amount of time spent outdoors or the importance of chronic indoor exposure.

That sensitization to inhalant allergens is common among patients with AD is now fully established. In addition there is sufficient experience from individual cases admitted to hospital or treated with allergen avoidance at home, and from challenge studies to

suggest that exposure to inhalants is an important factor in the disease. Indeed it is difficult to understand how a patient with >2,000 units of IgE ab to D. pteronyssinus, and excoriated skin lesions would not get symptoms from sleeping in a bed with high levels of dust mite allergen. Beck and Korsgaard demonstrated a dose-response relationship between exposure to house dust mites in bedding and dermatitis in adolescents and adults with AD (28). Our results show that 73% of older children were sensitized and that this process starts under the age of two. At present there is very little controlled evidence to demonstrate the efficacy of avoidance measures for inhalants in the treatment of AD; however this in large part reflects the difficulties of such controlled trials. The present results suggest that the correct design of such a controlled trial would be to enroll very young children presenting with eczema, food sensitivity, and elevated total IgE. The present results imply that avoidance measures should be for both dust mite and cat allergens, and that children should be followed to answer whether intervention can delay sensitization and/or reduce symptoms of eczema.

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FIGURE LEGENDS

Figure 1:

The prevalence of IgE antibody by RAST to five common inhalant allergens is shown for patients with atopic dermatitis and controls.

Figure 2:

The effects of age on specific IgE antibody to common inhalants in sera from AD patients (solid bars), control group 1 (right hatched bars), and control group II (vertical striped bars). A positive RAST was >40 U/ml of IgE ab to one or more allergens. Asterisk over AD bars represent significant p values for AD patients versus combined control groups I and II; ** $p<0.01$, and *** $p<0.001$.

Figure 3:

Seven children under two were sensitized to inhalant allergens by RAST. Their ages and IgE ab responses to specific allergens are demonstrated.

Figure 4:

Demonstrates specific RAST units for dust mite and cat allergens in AD patients, control group I, and control group II. AD patients are represented by solid symbols, and controls by open symbols.

Table I. Patient Characteristics

	AD	CONTROL I	CONTROL II#
number	61	33	57
mean age,years	4.1	5.4	7.9
age range,years	.5-13	.05-15.9	.5-16.1
male/female	62%/38%	45%/55%	59%/41%
race white	41%(42%)*	52%(40%)	67%(44%)
black	53%(53%)	48%(60%)	33%(56%)
other	6%(0%)	0%(0%)	0%(0%)
asthma	42%(28%)	9%(0%)	0%(0%)
rhinitis	28%(17%)	0%(0%)	- -
family history of allergic disease	92%(88%)	33%(20%)	44%(70%)

* Numbers in parenthesis represents values for children under two in each group.

Lack of asthma was an inclusion criterion for Control Group II.

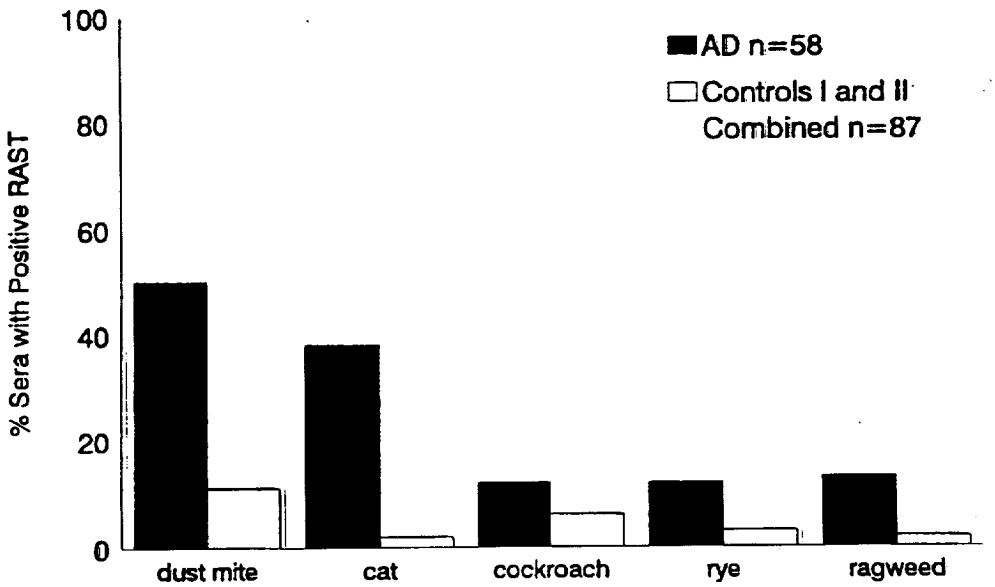
TABLE II. Univariate Odds Ratios For Various Risk Factors Associated With Atopic Dermatitis

RISK FACTORS	Univariate OR	95%CL
female sex	0.50	(.21-1.2)
black race	1.7	(.80-3.7)
family history	24.5	(7.0-85.5)*
positive RAST+	13.5	(3.7-48.9)*
Log IgE	65.7	(12.0-359.0)*
Eosinophil counts#	15.4	(2.8-84.6)*

* Denotes statistical significance.

+ RAST results from common inhalants.

n=22 AD patients and 33 controls



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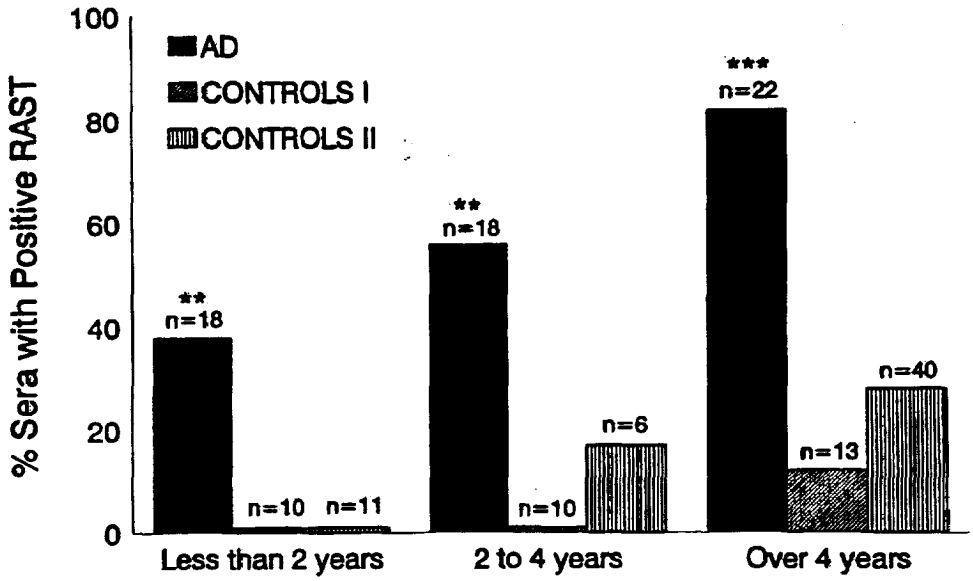

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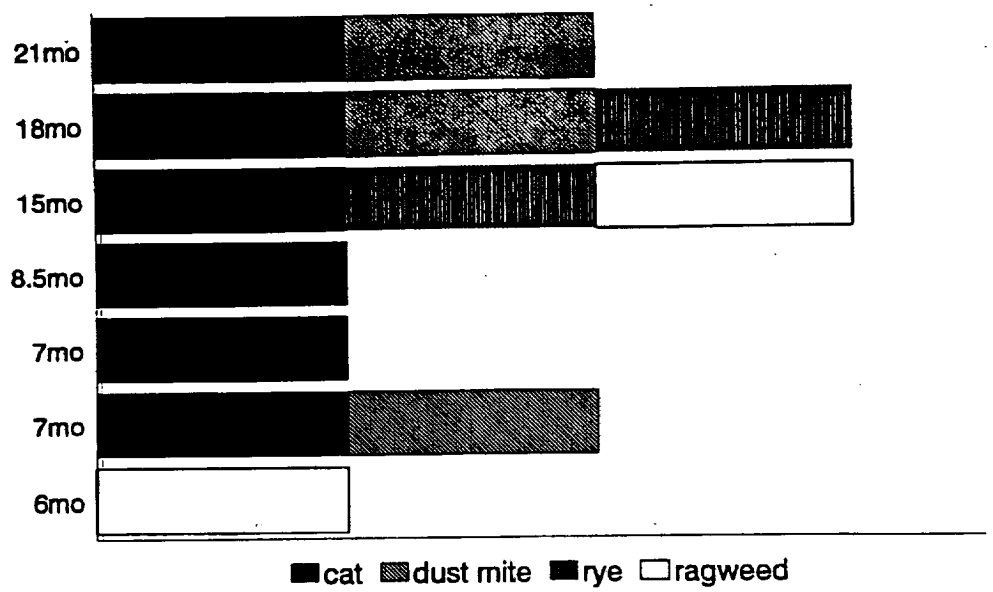

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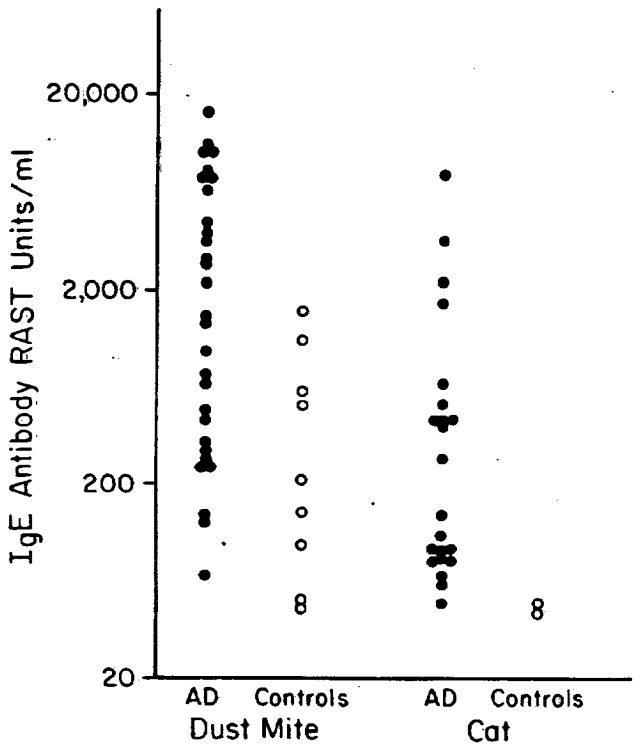

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